II.A.7.

Finally, the industry cites a study by Butschky *et al.*[233] to suggest that nicotine-free cigarettes cause "liking" too. What the industry does not mention is that the study was conducted in newly abstinent smokers and that these nicotine-free cigarettes were "liked" only when compared to lettuce cigarettes that the researchers acknowledged to be unpalatable. As described in section II.B.3., below, the repeated association of pharmacological effects and sensory effects over thousands of repetitions causes the sensory aspects of addictive behaviors (such as taste) to come to be associated with the pharmacological effect (such as "liking") of addictive substances. Much as Pavlov's dog salivated at the sound of the bell (a conditioned response), individuals addicted to drugs actually experience some of the effects of the psychoactive drug by conditioned cues associated with the act of self-administering the drug in the early stages of abstinence.[234] This phenomenon has been described for many drugs, including heroin.[235] Just as a heroin addict may experience a rush simply by injecting a saline solution, a cigarette smoker may experience pleasure when smoking a denicotinized cigarette. Thus, the finding that a denicotinized cigarette can trigger "liking" during withdrawal does not call into question the conclusion that nicotine has "subjective effects" in humans.

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[233] Butschky MF, Bailey D, Henningfield JE, *et al.*, Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers, *Pharmacology, Biochemistry and Behavior* 1995;50(1):91-96. *See* AR (Vol. 442 Ref. 7484).

[234] O'Brien CP, Testa T, Ternes J, *et al.*, Conditioning effects of narcotics in humans, in *Behavioral Tolerance: Research and Treatment Implications,* NIDA Research Monograph 18 (Washington DC: Government Printing Office No. 017-024-00899-8, Jan. 1978), at 67-71. *See* AR (Vol. 535 Ref. 96, vol. III.L).

[235] Surgeon General's Report, 1988, at 308-311. *See* AR (Vol. 129 Ref. 1592).

e. Comments on Self-Administration and Reinforcement

1. The tobacco industry argues that nicotine's reinforcing effects are different from those of heroin and cocaine, that animals need to be trained to self-administer nicotine, that the reinforcing efficacy of nicotine is more like that of caffeine, and that in one study cited by FDA a light stimulus associated with nicotine was required for self-administration. The industry concludes that animal self-administration studies do not support the finding that nicotine is addictive.

FDA disagrees. Upon review of the evidence in the administrative record, FDA notes that there are over ten studies demonstrating self-administration of nicotine by animals.[236] Only one of these is specifically contested by the tobacco industry. Furthermore, none of the industry's arguments seriously call into question FDA's finding that animals self-administer nicotine in a manner consistent with other addictive substances.

It is true that the reinforcing effects of nicotine do differ from those of cocaine and heroin; all dependence-producing drugs are not alike. In fact, FDA noted that the range of environmental conditions under which nicotine functions as a positive reinforcer appears more limited than for cocaine.[237] The limited conditions under which animals self-administer nicotine, however, closely correspond to the conditions of human tobacco use. That is, animals self-administer nicotine when it is given intermittently—in a fashion similar to nicotine delivery from cigarettes and smokeless tobacco.

[236] *See* appendix 1 to Jurisdictional Analysis. *See* AR (Vol. 1 Appendix 1).

[237] *Id.*

II.A.7.

FDA agrees that animals can be trained to self-administer nicotine. This method is widely accepted as standard practice in self-administration testing in animals. What is important is that, under these conditions, nicotine is self-administered significantly more than placebo and in a manner consistent with other addictive substances.

The tobacco industry cites a review chapter in a textbook on psychopharmacology to suggest that caffeine and nicotine self-administration are similar. The review article cited focuses on whether caffeine is a drug of abuse and, while casually noting similarities between some data on nicotine and caffeine, does not purport to analyze the studies on nicotine at all.[238] Indeed, caffeine self-administration in animals is weak and sporadic.[239] FDA further notes that the chapter on nicotine in this same textbook unequivocally concludes that nicotine is addictive.[240]

Finally, FDA agrees that the study by Goldberg *et al.*[241] showed that squirrel monkeys self-administer nicotine most actively when associated with a light stimulus. The tobacco

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[238] Griffiths RR, Mumford GK, Caffeine—A drug of abuse?, in *Psychopharmacology: The Fourth Generation of Progress*, eds. Bloom FE, Kupfer DJ (New York: Raven Press, 1995), at 1699-1713. *See* AR (Vol. 535 Ref. 96, vol. III.E).

[239] Heishman SJ, Henningfield JE, Stimulus functions of caffeine in humans: relation to dependence potential, *Neuroscience and Biobehavioral Reviews* 1992;16:273-287. *See* AR (Vol. 79 Ref. 230).

Griffiths RR, Woodson PP, Reinforcing properties of caffeine: studies in humans and laboratory animals, *Pharmacology, Biochemistry and Behavior* 1988;29(2):419-427. *See* AR (Vol. 535 Ref. 96, vol. III.E).

Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 524. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[240] Henningfield JE, Schuh LM, Jarvik ME, Pathophysiology of tobacco dependence, in *Psychopharmacology: The Fourth Generation of Progress*, eds. Bloom FE, Kupfer DJ (New York: Raven Press, 1995), at 1715-1729. *See* AR (Vol. 39 Ref. 72).

[241] Goldberg SR, Spealman RD, Goldberg DM, Persistent behavior at high rates maintained by intravenous self-administration of nicotine, *Science* 1981;214:573-575. *See* AR (Vol. 5 Ref. 35-2).

industry implies that this finding means that the light stimulus—not nicotine—was responsible for nicotine self-administration in this study. FDA disagrees. Rates of self-administration of nicotine with the light stimulus *were markedly higher than rates of self-administration of placebo* with the light stimulus. Indeed, the monkeys' self-administration of nicotine was so intense that it resembled cocaine use. Thus, the conclusion that nicotine was not self-administered is incorrect; the correct conclusion is that nicotine self-administration was most dramatic when associated with environmental cues that had been linked to nicotine injections.

2. The smokeless tobacco industry claims that its products provide a constant dose of nicotine, a regimen that animals did not self-administer. This claim is contrary to the evidence. As described in section II.D., below, moist snuff and chewing tobacco do not provide uniform release of nicotine from the products. In fact, each pinch of smokeless tobacco provides nicotine that is absorbed rapidly for the first 5 minutes; the rate of absorption then tapers off until the next pinch is consumed. This pattern of nicotine consumption is similar to the regimen that was self-administered by animals.

3. The tobacco industry criticizes the human self-administration study conducted by Henningfield *et al.*[242] on the grounds that the number of subjects used in the study was too small, that the study should have been conducted with subjects without a history of drug abuse, and that the subjects also self-administered saline.

FDA believes that the study's design was sound and that the results are reliable. The procedure utilized by these researchers is the standard procedure utilized by all investigators evaluating the abuse liability of a compound in humans. This well-

[242] Henningfield JE, Miyasoto K, Jasinski DR, Cigarette smokers self-administer intravenous nicotine, *Pharmacology, Biochemistry and Behavior* 1983;19:887-890. *See* AR (Vol. 39 Ref. 71).

established procedure has been used to examine the abuse potential of a variety of compounds, such as alcohol, marijuana, heroin, and sedatives, in both inpatient and outpatient settings. In the evaluation of a new molecular entity (NME) that shows some structural and/or pharmacological similarities to known drugs of abuse, FDA requires that studies similar to this one be conducted in order to reach a regulatory decision on the abuse potential of the NME being considered for drug approval.[243]

In response to the concerns of the tobacco industry about the study methodology, the sample size of six is acceptable and the use of volunteers with histories of drug abuse is a valid method of conducting such research, according to the National Institute on Drug Abuse.[244] Human studies evaluating the abuse potential of a compound in subjects without a history of drug abuse do not produce valid results. Such tests in non-drug abusers could lead to the conclusion that drugs, including heroin, have a low potential to produce dependence because first-time users may not find them pleasant.[245]

With respect to the self-administration of saline, the comment overlooks major distinctions between nicotine and saline: (1) "subjective effects" were not associated with the saline deliveries, thus saline was not psychoactive; (2) in comparison to the orderly pattern of self-administration observed with the nicotine injections, the pattern of saline deliveries was highly variable; (3) the number of self-administered saline injections

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[243] *See* Surgeon General's Report, 1988, at 270. *See* AR (Vol. 129 Ref. 1592).

[244] Jasinski DR, Henningfield JE, Human abuse liability assessment by measurement of subjective and physiological effects, in *Testing for Abuse Liability of Drugs in Humans*, eds. Fischman MW, Mello NK, NIDA Research Monograph 92 (Rockville MD: National Institute on Drug Abuse, 1989). *See* AR (Vol. 76 Ref. 172).

[245] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573), at 529. *See* AR (Vol. 535 Ref. 96, vol. III.G).

decreased across sessions while nicotine injections were constant in those subjects who were tested repetitively with saline and nicotine; and (4) when saline and nicotine were simultaneously available in a follow-up study, the volunteers self-administered nicotine almost exclusively and not saline.[246] Thus, saline was not psychoactive and did not function as a "positive reinforcer."

4. The tobacco industry argues that caffeine, rapid eye movement (REM) sleep, magnetic fields, and stress increase dopamine levels in the brain. According to the industry, then, nicotine's effect on dopamine activity is shared by several other compounds or experiences.

This argument is based on a mischaracterization of the relationship between addictive substances and dopamine activity. FDA found that nicotine and other addictive substances do more than increase dopamine levels in the brain; they increase dopamine activity in a specific system that signals reward and pleasure, thus leading to reinforcing behavior. Nicotine's effect in this system is similar to that of other dependence-producing substances. These conclusions are based on reproducible studies and are widely accepted in the scientific community. Indeed, none of the industry's cited studies casts any doubt on the profound effects of nicotine on this brain system.

One study, cited by the industry as proof of the effect of caffeine on dopamine levels, actually examined the effect of caffeine on aggressive behavior of rats. Dopamine levels were not even measured. The authors merely speculated at the end of the article

[246] Surgeon General's Report, 1988, at 192. *See* AR (Vol. 129 Ref. 1592).

that caffeine may affect rat aggression via dopamine. Moreover, they did not extend their speculation to reward or reinforcement.[247]

Another study, cited by the industry as proof of the effect of REM sleep and magnetic fields on dopamine, actually described two patients treated with magnetic fields—without any control group. The authors merely speculated that REM sleep deprivation and magnetic fields may affect dopamine in the mesolimbic system. But without a control group, it is impossible to assess whether there was *any* true response to magnetic fields.[248]

The industry cites a third study to suggest that stress increases dopamine levels.[249] This study delivered severe stimuli such as electric shocks to mice and studied dopamine responses. The authors concluded that a dopamine-based reward pathway exists and is altered under conditions of severe stress. This conclusion casts no doubt on the finding that nicotine also critically affects this pathway.

5. In a footnote, the tobacco industry argues that "it is not clear that nicotine's effects on dopaminergic mechanisms play a significant role in smoking behavior." This argument refers to a study by Corrigall and Coen.[250]

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[247] Petkov VV, Rousseva S, Effects of caffeine on aggressive behavior and avoidance learning of rats with isolation syndrome, *Methods and Findings in Experimental and Clinical Pharmacology* 1984;6(8):433-436. *See* AR (Vol. 535 Ref. 96, vol. III.L).

[248] Sandyk R, Tsagas N, Anninos PA, *et al.*, Magnetic fields mimic the behavioral effects of REM sleep deprivation in humans, *International Journal of Neuroscience* 1992;65(1-4):61-68. *See* AR (Vol. 535 Ref. 96, vol. III.L).

[249] Puglisi-Allegra S, Kempf E, Cabib S, Role of genotype in the adaptation of the brain dopamine system to stress, *Neuroscience and Biobehavioral Reviews* 1990;14(4):523-528. *See* AR (Vol. 535 Ref. 96, vol. III.L).

[250] Corrigall W, Coen K, Dopamine mechanisms play at best a small role in the nicotine discriminative stimulus, *Pharmacology, Biochemistry and Behavior* 1994;48(3):817-820. *See* AR (Vol. 535 Ref. 96, vol. III.B).

FDA has reviewed the study in question and concludes that the tobacco industry's conclusion seriously misrepresents the research. In this paper, the authors suggested that dopamine activity may not explain why smokers recognize low doses of nicotine in their brain, but the authors never doubted that dopamine activity is essential to the reward associated with smoking. The same article cited by the industry includes the statement that "the reinforcing effects of nicotine have a dopaminergic substrate, likely the ascending mesolimbic dopamine system"[251]—exactly the finding of FDA. These researchers, misrepresented by the industry to suggest a small role for dopamine in smoking behavior, have demonstrated in their own laboratory that dopamine activity significantly affects nicotine consumption.[252]

f. Comments on Withdrawal, Tolerance, and Nicotine Replacement

1. The tobacco industry argues that the effects of withdrawal from nicotine are not substantial. This argument is based upon multiple overlapping and sometimes contradictory contentions: (1) nicotine withdrawal is not as severe as withdrawal from certain other drugs, and some people quit smoking easily; (2) physical and psychological symptoms experienced during nicotine withdrawal are not the same among all abstinent users; (3) withdrawal from nicotine produces psychological but not physical symptoms; (4) the psychological symptoms of abstinence may actually be a psychopathological condition previously suppressed by nicotine or may be frustration with losing a pleasurable activity; (5) what is thought to be nicotine withdrawal may actually be caffeine withdrawal

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[251] *Id.* at 817.

[252] Corrigall WA, Franklin KBJ, Coen KM, *et al.*, The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine, *Psychopharmacology* 1992;107:285-289. *See* AR (Vol. 8 Ref. 93-4).

or caffeine toxicity; (6) the severity of withdrawal symptoms does not always correlate with relapse; and (7) epidemiological studies cited by FDA do not prove a substantial withdrawal syndrome.

Upon careful review of the industry's comments and the administrative record, FDA finds that nicotine clearly produces a withdrawal syndrome among abstinent tobacco users. This syndrome—which includes both psychological and physiological symptoms—is described in numerous scientific articles and reviews cited by FDA,[253] only a few of which were criticized by the tobacco industry. Of the studies on withdrawal from smokeless tobacco cited by FDA, none is contested by the industry. The tobacco industry also accepts FDA's finding that tobacco withdrawal causes many significant autonomic changes, such as changes in heart rate. Several of the industry's arguments do not seriously contest the fact that nicotine has a substantial withdrawal syndrome. The remaining arguments contradict each other. The Agency's specific responses to the major industry contentions are as follows:

- Nicotine withdrawal is not as severe as withdrawal from certain other drugs, and some people quit smoking easily.

FDA agrees that withdrawal from nicotine is not as acutely life-threatening as withdrawal from certain addictive drugs such as alcohol or short-acting barbiturates. But the severity of nicotine withdrawal *is* comparable to that of other addictive drugs such as

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[253] *See* Jurisdictional Analysis, 60 FR 41560–41562

See also Surgeon General's Report, 1988, at 197-207. *See* AR (Vol. 129 Ref. 1592).

American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 244-245. *See* AR (Vol. 37 Ref. 8).

cocaine.[254] Medical authorities around the world have recognized the existence of a nicotine withdrawal syndrome that causes "clinically significant distress or impairment in social, occupational, or other areas of functioning."[255]

FDA agrees that some people quit tobacco products easily. Similarly, some people quit cocaine and other addictive substances easily.[256] However, for most addicted users of tobacco, quitting is very difficult. *See* section II.A.3.c.ii., above. The characteristic feature of an addictive substance is that it is difficult for most people to quit. Thus, the fact that some people can quit smoking easily is irrelevant to nicotine's addictiveness and to the scientific consensus supporting a nicotine withdrawal syndrome. Moreover, it may actually be easier to quit other powerful substances than to quit nicotine. Smokers who consume about a pack or more of cigarettes per day are more than twice as likely to report withdrawal symptoms during abstinence as people who consume five or more drinks on five or more occasions in a month, people who repeatedly use cocaine, and people who repeatedly use marijuana.[257]

- Physical and psychological symptoms experienced during nicotine withdrawal are not the same among all abstinent users.

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[254] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437, at 429. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[255] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 245. *See* AR (Vol. 37 Ref. 8).

[256] Kleber H, Don't you believe that nicotine isn't addictive, *New York Times*, Apr. 4, 1994. *See* AR (Vol. 196 Ref. 2497).

Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437, at 429. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[257] Henningfield JE, Clayton R, Pollin W, Involvement of tobacco in alcoholism and illicit drug use, *British Journal of Addiction* 1990;85:279-292, at 280-281. *See* AR (Vol. 39 Ref. 66).